IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SHIRE ORPHAN THERAPIES LLC and SANOFI-AVENTIS DEUTSCHLAND GMBH,	)	
Plaintiffs,	)	
v.	)	C.A. No. 15-1102-GMS
FRESENIUS KABI USA, LLC,	)	
Defendant.	)	

PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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TABLE OF EXHIBITS HAVING SHORT TITLES

Exhibit #	Short Title	Reference
Joint Trial Exhibits ("JTX")		
JTX-1	the '333 patent	Certified U.S. Patent No. 5,648,333
JTX-9	Kyle I	Kyle et al., *Design and Conformational Analysis of Several Highly Potent Bradykinin Receptor Antagonists*, 34 J. Med. Chem. 1230-1233 (1991)
JTX-15	Bodanszky (excerpt)	Bodanszky, Peptide Chemistry: A Practical Textbook, Berlin, DE: Springer-Verlag (1988) (Excerpted)
JTX-38	the '963 patent	U.S. Patent No. 4,923,963
JTX-39	Kinin Antagonists	Barabé et al., *Kinin Antagonists*, 163 Meth. Enzymol. 282-292 (1988)
JTX-40	the '204 patent	U.S. Patent No. 4,837,204
JTX-41	Farmer	Farmer et al., *D-Arg[Hyp3-Thi5-D-Tic7-Tic8]-bradykinin, a potent antagonist of smooth muscle BK2 receptors and BK3 receptors*, 102 Br. J. Pharmacol. 785-787 (1991)
Plaintiffs' Trial Exhibits ("PTX")		
PTX-072	M.P.E.P. § 608.01(p)	M.P.E.P. § 608.01(p) (5th ed. Rev. 13, Nov. 1989)
PTX-073	Updated Utility Guidelines	Request for Comments on Proposed Utility Examination Guidelines, 60 Fed. Reg. 97-98 (Jan. 3, 1995)
Defendant's Trial Exhibits ("DTX")		
DTX-050	Wirth (1991)	Wirth et al., *Hoe 140 A New Potent and Long Acting Bradykinin-Antagonist: In Vivo Studies*, 102 Br. J. Pharmacol. 774-777 (1991)
DTX-059	the '7,803 patent	U.S. Patent No. 5,597,803

TABLE OF PATENT APPLICATIONS HAVING SHORT TITLES

Term	Short Title
'162 application	USSN 07/374,162
'149 CIP application	USSN 07/746,149
'052 application	USSN 07/982,052
'270 application	USSN 07/565,270
'090 CIP application	USSN 07/837,090
'297 application	USSN 07/690,297
'766 application	USSN 07/841,766
'523 application	USSN 07/969,523
'849 CIP application	USSN 08/012,849
'018 application	USSN 08/236,018
'442 application	USSN 08/487,442

I. INTRODUCTION

This case concerns claim 14 of the '333 patent, which covers the peptide icatibant. D.I. 80; D.I. 94, Ex. 2: Proposed Statement of Uncontested Facts ("UF")[1] ¶ 34. Plaintiff Sanofi-Aventis Deutschland GmbH owns the '333 patent. Icatibant is the active pharmaceutical ingredient in Plaintiff Shire Orphan Therapies LLC's[2] FIRAZYR® (icatibant injection) product ("FIRAZYR"), approved by the FDA on August 25, 2011 for the treatment of acute attacks of hereditary angioedema ("HAE") in adults 18 years and older. FIRAZYR is a preparation of icatibant that is supplied in a pre-filled syringe for self-administered, subcutaneous injection.

Defendant Fresenius Kabi USA, LLC ("Fresenius") admits infringement of claim 14, but alleges it is invalid for obviousness-type double patenting ("OTDP") in view of claim 1 of the '7,803 patent, and that it is unenforceable under the doctrine of prosecution laches. The law and evidence of record do not support Fresenius's allegations.

Fresenius's OTDP argument—removal of the N-terminal modification Fmoc from the peptides of claim 1 of the '7,803 patent to result in claim 14 of the '333 patent—oversimplifies the facts, ignoring relevant disclosures in the intrinsic record and prior art. Claim 1 of the '7,803 patent itself, as well as the specification, undeniably demonstrate that N-terminal modifications like Fmoc are intended to be permanent and integral components of the final peptide product. The prior art establishes that N-terminal modifications confer beneficial biological attributes to peptides, including bradykinin antagonists. In view of this evidence, a person of ordinary skill in the art ("POSA") would not have been motivated to remove the N-terminal modification from the peptides of claim 1 of the '7,803 patent to result in claim 14 of the '333 patent. And even if a

[1] Plaintiffs incorporate by reference the Proposed Statement of Uncontested Facts.

[2] Plaintiff Sanofi-Aventis Deutschland GmbH and Plaintiff Shire Orphan Therapies LLC are collectively referred to collectively as "Plaintiffs."

POSA had done so, a POSA still would not have arrived at the peptide of claim 14 composed of the amino acids D-Tic and Oic. As of 1989, neither D-Tic, nor Oic, nor any other bicyclic conformationally constrained amino acid had been incorporated into a bradykinin analog. Because a POSA would not have known whether a peptide appearing to be a bradykinin analog with D-Tic at position 7 and Oic at position 8 would be a bradykinin antagonist, a POSA would have modified positions 7 and 8 in accordance with the teachings of the relevant literature. Fresenius's OTDP allegation must fail—there is not clear and convincing evidence that claim 14 of the '333 patent is an obvious variant of claim 1 of the '7,803 patent.

Evidence of objective indicia undercuts Fresenius's OTDP argument. Fresenius did not rebut testimony by Dr. Kaplan[3], a world-renowned HAE expert with over forty years of clinical experience, of the long-felt need met by icatibant. Evidence further establishes that the safety, efficacy, and convenience afforded by icatibant have made FIRAZYR a commercial success.

Regarding laches, Fresenius cannot show that applicants unreasonably and inexplicably delayed prosecution of the '333 patent—during the four-year alleged delay, applicants pursued three distinct inventions, advanced prosecution by adding examples and data, amended claims, overcame OTDP rejections, and acted in a manner typical of biotechnology applicants at the time. In addition, the *in vivo* data in Wirth (1991) did not have to be submitted to the USPTO earlier because it had already been considered by the examiner and related to one species only. Nor has Fresenius provided *any* evidence that any single party had intervening rights during the alleged period of delay that were adversely affected by the alleged delay.

II. PLAINTIFFS' PROPOSED FINDINGS OF FACT

A. The '333 Patent Concerns Bradykinin Antagonists

1. Claim 14 is directed to the decapeptide icatibant (Walensky Tr. 553:7-10; UF ¶

[3] Photos of witnesses and related information are in Appendix A.

34; JTX-1 at 44:44-46)[4], which is a bradykinin antagonist that prevents native bradykinin from binding to its receptor. Walensky Tr. 498:5-10. Icatibant was synthesized on January 11, 1989 (PTX-011T.48, 52-56) and was determined to be a bradykinin antagonist on January 19, 1989 (PTX-012.24-27; JTX-1 at 16:37-17:9 (Table 1); Wirth Tr. 450:3-451:11, 456:23-457:9).

2. Based on relevant facts (Walensky Tr. 493:20-496:5), a POSA in the context of the '333 patent is a person who has at least a Ph.D. in organic chemistry, medicinal chemistry, pharmacology, or a similar field, and has a working knowledge of the chemistry and biochemistry of bradykinin or other peptides for the purposes of drug development. *Id.*[5]

3. The specification of the '333 patent is limited to bradykinin antagonists. *Id.* at 497:15-499:21; JTX-1 at JTX-1.2, 1:44-45, 1:53-54, 16:37-17:9 (Table 1). As such, a POSA would have interpreted claim 14 as the identified peptide having bradykinin antagonist activity.[6] Walensky Tr. 496:15-24, 499:22-500:2; JTX-1 at 44:44-46. Icatibant acetate is the active ingredient in FIRAZYR (Kaplan Tr. 432:18-433:2), and is covered by claim 14.

B. Claim 14 of the '333 Patent Is Not Invalid for Obviousness-type Double Patenting Over Claim 1 of the '7,803 Patent in View of the Prior Art

4. In October 1991, Dr. Wirth of Sanofi's predecessor Hoechst reported on "sticky compounds," which bind to the receptor tightly, thus providing longer duration of action and possibly increased metabolic stability. Wirth Tr. at 461:6-22, 462:21-463:2, 464:11-465:18; PTX-061T.7; Bachovchin Tr. 201:3-8. Research related to these sticky compounds resulted in

[4] Citation formats are: trial transcript as [Witness Name] Tr. [Page(s)]:[Line(s)]; exhibits other than patents as [Exhibit No.].[Page]; patents as [Exhibit No.] at [Column]:[Line(s)].

[5] The definition of a POSA is disputed. Bachovchin Tr. 55:14-56:4, 56:11-14. Dr. Walensky's ultimate opinion regarding OTDP would not change even if the Court adopts Dr. Bachovchin's definition of POSA. Walensky Tr. 496:6-10.

[6] The meaning of claim 14 of the '333 patent is disputed. Bachovchin Tr. 99:4-101:1. Dr. Walensky's ultimate OTDP opinion would not change even if the Court adopts Dr. Bachovchin's definition of claim 14. Walensky Tr. 500:3-7.

the '7,803 patent. Wirth Tr. at 466:8-468:11; DTX-059; PTX-061T.7. The '7,803 patent discloses bradykinin antagonists with lipophilic N-terminal modifications (i.e., "sticky compounds") such as Fmoc. Wirth Tr. at 467:7-13, 468:12-19; DTX-059 at 18:43-45. By contrast, the peptide of claim 14 of the '333 patent, icatibant (JTX-1 at 44:44-46), is not a sticky compound (Wirth Tr. 466:3-7) and is not N-terminally modified (*id.* at 468:20-21).

i. A POSA Would Have Understood the Language of Claim 1 of the '7,803 Patent to Mean that the N-terminal Modifications of the Claimed Peptides Should Not Be Removed

5. Claim 1 of the '7,803 patent claims "[a] peptide of the formula I," which is "Z-P-A-B-C-E-F-K-(D)Q-G-M-F'-I" ("a peptide of the formula I"; Walensky Tr. 501:22-502:1). DTX-059 at 20:22-49. From just the claim language, a POSA would have interpreted "Z" as an N-terminal modification that is an integral and permanent component of the final and claimed peptide product. Walensky Tr. 500:18-501:1, 548:17-21. The meaning of "Z", which can be the chemical moiety Fmoc (*id.* at 502:20-503:3; DTX-059 at 20:22-49), is disputed.[7]

6. The plain language of claim 1 requires that the Z component must be one of eleven chemical moieties. Walensky Tr. 502:16-503:13; DTX-059 at 20:28-33. In clear contrast, claim 1 permits component "P" to be one of six chemical moieties or a "direct linkage" (i.e., a chemical bond; no chemical moiety). Walensky Tr. 503:4-6, 505:1-12; Bachovchin Tr. 205:22-206:3; DTX-059 at 20:34-35. Having no chemical moiety (i.e., having nothing) is not an option for Z, which demonstrates that Z is a permanent part of the peptide. Walensky Tr. 503:7-19, 505:8-16, 548:17-21; Bachovchin Tr. 206:4-6; DTX-059 at 20:28-33.

7. Moreover, all eleven moieties for Z share a common chemical feature, an acyl

[7] Dr. Bachovchin's position, contrary to Dr. Walensky's, is that a POSA just looking at claim 1 would understand that the purpose of the Z group could be for multiple reasons (Bachovchin Tr. 143:17-24, 146:15-19), including that the Z group could "be left over from synthesis and would therefore think that it should be removed" (*id.* at 147:7-15; *see also id.* at 148:14-17).

group. Walensky Tr. 502:12-15, 503:20-504:21. This shared feature is indicative of the permanence of the Z group. *Id*. Fmoc, one option for Z, is also classified as a urethane aromatic group due to the presence of an oxygen atom. *Id.* at 503:20-504:21.

8. The meaning of "P" in a peptide of the formula I is disputed.[8] Based upon the claim language, a POSA would have understood that P could be one of six chemical moieties or a direct linkage (*id.* at 503:4-6, 505:1-12; Bachovchin Tr. 205:22-206:3), with no one option prioritized over another. Walensky Tr. at 509:1-11; DTX-059 at 20:34-35. This interpretation is consistent with the examples (Walensky Tr. 505:25-506:25; DTX-059 at 18:31-20:20) and biological data (Walensky Tr. 507:1-508:25; DTX-059 at 14:28-15:26 (Table 1), 15:35-50 (Table II) in the '7,803 patent.

ii. Claims 2 and 3 and the Specification of the '7,803 Patent Confirm that the N-terminal Modifications of the Claimed Peptides Are Permanent and Integral Components that Are Not to Be Removed

9. Claim 2 concerns the administration of an "effective amount of a peptide of the formula I **as claimed in claim 1**" and claim 3 is directed to a "pharmaceutical composition containing a peptide of the formula I **as claimed in claim 1**." DTX-059 at 20:50-57 (emphasis added). Both claims 2 and 3 require the complete peptides of the formula I as claimed, including the Z group. Walensky Tr. 509:24-510:21; DTX-059 at 20:50-57.

10. The specification of the '7,803 patent also is informative as to the meaning of Z in a peptide of the formula I.[9] Walensky Tr. 509:12-23, 548:22-24. Both the title and abstract

[8] Dr. Bachovchin's position, contrary to Dr. Walensky's, is that compared to the direct linkage, the amino acids identified for P are "probably less significant for the desired biological properties" (Bachovchin Tr. 151:2-10), and that a POSA would view a peptide of formula I first as a ten amino acid peptide (i.e., P being a direct linkage) and secondarily as an eleven amino acid peptide (i.e., P being a chemical moiety) (*id.* at 151:11-19).

[9] Dr. Bachovchin did not consider the specification or the prosecution history of the '7,803 patent to construe claim 1 of the '7,803 patent. Bachovchin Tr. 140:22-141:13.

identify the peptides of the '7,803 patent as having N-terminal modifications (Z). *Id.* at 510:22-511:12; DTX-059.1. In addition, every example of a peptide of formula I contains Z (Walensky Tr. 511:13-512:1; DTX-059 at 18:32-20:20), and every peptide evaluated for biological activity has a Z group. Walensky Tr. 512:2-11; DTX-059 at 14:28-15:26 (Table I).

11. The description of the synthesis of peptides of the formula I using Fmoc solid-phase peptide synthesis in the specification is highly instructive as to the meaning of the "Z" group. Walensky Tr. 512:12-519:5; DTX-059 at 10:24-13:17, 18:32-19:24. In the context of peptide synthesis, Fmoc is a protecting group that shields the amino group of each amino acid as it is added to the growing peptide chain. Walensky 512:22-514:9, 515:12-516:12; DTX-059 at 10:31-34, 10:63-67, 11:9-19, 13:13-15, 18:35-62. After an N-protected amino acid is added, Fmoc is removed. *Id.* This process is repeated until the last amino acid is added to the peptide. *Id.* By contrast, for peptides of the formula I with Fmoc as Z, Fmoc is not removed and is part of the final peptide product. Walensky Tr. 514:10-515:6, 516:13-517:4; DTX-059 at 18:62-67.

12. The specification of the '7,803 patent contemplates two strikingly different functional roles for Fmoc: (1) a protecting group used during synthesis that is removed from a peptide under construction while that peptide is attached to the resin and/or still has side chain protective groups; or (2) an integral component of the final peptide product. Walensky Tr. 517:19-519:5. The prior art is consistent with this teaching in the '7,803 patent; removal of Fmoc from a peptide in the prior art of record occurs only when the peptide is under construction, i.e., when a peptide is on the resin and/or contains protective side chain groups. Bachovchin Tr. 151:20-162:4; JTX-16.2-3; DTX-015 at 23:5-24:19; DTX-060.1-4. Dr. Knolle, an inventor on both the '333 and '7,803 patents, also recognized that Fmoc could be used as a protecting group

or left on the peptide. Knolle Tr. 298:13-19; 300:2-302:16.[10]

13. Fresenius alleges that peptides of the '7,803 patent with Fmoc at the N-terminus resemble intermediates made during peptide synthesis, suggesting that a POSA would have been motivated to remove the Fmoc. Tr. 17:2-4. But such peptides are not intermediates as they are not under construction, i.e., not on a resin and do not contain side chain protecting groups. Bachovchin Tr. 141:14-143:16; Walensky Tr. 607:22-609:16. Moreover, during prosecution that led to the '7,803 patent the applicants distinguished peptide intermediates under construction having Fmoc and side chain protective groups from the peptides of the claims. DTX-055.218. The examiner agreed with the applicants and allowed the claims. *Id.* at 238.

iii. The Prior Art Taught the Use and Benefits of Permanent N-terminal Modifications on Peptides, Including on Bradykinin Antagonists

14. Contrary to Fresenius's arguments, a POSA would not have been motivated to remove the N-terminal modifications from the peptides of claim 1 of the '7,803 patent because as of 1989 it was already known[11] that the addition of these N-terminal modifications could confer significant benefits to the resulting peptide, including reduction of side effects and resistance to enzymatic degradation. Walensky Tr. 519:9-520:3, 548:9-16, 548:25-549:4.

15. The Kinin Antagonists article demonstrates how acetylation at the N-terminus of bradykinin antagonists could reduce or eliminate the side effect of histamine release (*id.* at 524:18-525:8), while additional modifications could reduce undesired agonist activity (*id.* at 525:9-526:4). JTX-39.11. The article exemplifies a bradykinin antagonist with multiple modifications at the N-terminus, namely D-Arg at position 0, which is then acetylated. Walensky

[10] Dr. Jacobsen, who submitted an expert report in this case, but did not appear at trial, indicated in his deposition that if a chemist planned to remove Fmoc he would know how to do so. Walensky Tr. 578:8-579:20.

[11] This prior art includes the Kinin Antagonists article (JTX-39), the '963 patent (JTX-38), the '204 patent (JTX-40), and Bodanszky (excerpt) (JTX-15).

Tr. 526:5-24, 609:17-610:3; JTX-39.11 (Table V). Kinin Antagonists provides a basis for why a POSA would not have been motivated to remove N-terminal modifications from the peptides of formula I of the '7,803 patent. Walensky Tr. 524:8-17.

16. The '963 patent recommends "N-terminal enzyme protecting group[s] selected from the group comprising acyl-type protecting groups [and] aromatic urethane-type protecting groups" on bradykinin antagonists to confer enzymatic resistance. Walensky Tr. 520:15-521:11; JTX-38 at 1:11-21, 4:1-10, 5:1-57 (Table I, Table II). It also includes examples of peptides with an acetyl group at the N-terminus. Walensky Tr. 521:20-522:4; JTX-38 at 5:1-57 (Tables I, II), 12:1-3, 13:16-19, 13:33-36. Biological data demonstrate that bradykinin analogs with an acetyl group could convert a weak bradykinin agonist into an antagonist. Walensky Tr. 522:5-524:1; JTX-38 at 17:36-20:50 (Table V). The '963 patent provides a basis for why a POSA would not have been motivated to remove N-terminal modifications, such as the acyl- and urethane-type Z groups, from the peptides of formula I of the '7,803 patent. Walensky Tr. 521:12-15.

17. The '204 patent teaches N-terminal modifications to, among other things, "protect the N-terminus against undesirable reactions during synthetic procedures or to prevent the attack of exopeptidases on the final compounds . . . ." *Id.* at 526:25-528:1; JTX-40 at 3:1-6. In the former case, the N-terminal group is removed so that it is not part of the final product, whereas in the latter case it is not removed and would remain part of the final compound. Bachovchin Tr. 162:5-164:1. A non-exhaustive list of the same chemical moieties suggested for use at the N-terminus for either of these objectives "includes but is not limited to acyl, acetyl, . . . t-butyloxycarbonyl(Boc), carbobenzyloxycarbonyl or benzoyl groups or an L- or D- aminoacyl residue, which may itself be N-protected." Walensky Tr. 528:1-11; Bachovchin Tr. 165:9-14; JTX-40 at 3:6-10. The phrase "which may itself be N-protected" indicates that a D-amino acid

added to the N-terminus may be further modified with an acetyl or acyl group. Walensky Tr. 528:7-18, 610:4-15.

18. Notably, the '204 patent identifies Boc and carbobenzyloxycarbonyl groups, both routinely used as N-terminal protecting groups during peptide synthesis like Fmoc (Bachovchin Tr. 164:16-165:8), as options for N-terminal modifications in a final product to protect against enzymatic degradation. JTX-40 at 3:1-10. It provides examples of compounds having Boc at the N-terminus of an amino acid in a final product. Bachovchin Tr. 165:24-167:17; JTX-40 at 8:17-40, 29:36-60. Dr. Bachovchin himself even used Boc at the N-terminus of final peptidic molecules in the 1980's. Bachovchin Tr. 167:18-171:3.

19. Like the peptidic compounds of the '204 patent, the peptides of formula I of the '7,803 patent have permanent N-terminal modifications (Z) that are acyl, acetyl, benzoyl, and other moieties routinely used in peptide synthesis. *Id.* at 150:12-151:1; Walensky Tr. 528:6-9. The '204 patent provides a basis for why a POSA would not have been motivated to remove N-terminal modifications from peptides of formula I of the '7,803 patent. Walensky Tr. 527:22-25.

20. In considering amine-protecting groups in peptide synthesis, Bodanszky states that it is obvious that certain groups are not suitable; for example "acetylation or benzoylation of amino groups is impractical, because the vigorous hydrolysis needed for deacylation cleaves peptide bonds as well." *Id.* at 528:19-529:6; JTX-15.31. This speaks to the permanence of the Z groups of the peptides of formula I of the '7,803 patent, which include acetyl and benzoyl groups. Walensky Tr. 529:7-24; Bachovchin Tr. 150:12-151:1.

iv. Bradykinin Researchers Used Fmoc as an Integral and Permanent Component of an Active Ingredient that Advanced to Clinical Trials

21. In 1989 Nova Pharmaceutical Corp. ("Nova")[12] discovered and gave high priority

[12] Nova was a company involved in bradykinin antagonist research. PTX-353.3.

to researching compounds used to treat inflammatory diseases (PTX-353.3, 11) called leumedins, a series of amino acids containing Fmoc in the ultimate active ingredient—the same Fmoc moiety used in peptide synthesis and as an N-terminal Z group of the peptides of formula I of the '7,803 patent. Bachovchin Tr. 171:8-173:11. Nova investigated NPC 15199 (*id.* at 173:12-174:21; PTX-353.3, 11), which was simply Fmoc attached to the standard amino acid leucine (Bachovchin Tr. 172:12-25), and advanced it into clinical trials in April 1990. Burch Tr. 256:22-257:14. It was recommended that Nova's bradykinin antagonist program be stopped in favor of the leumedins. *Id.* at 255:1-18. The leumedins displayed a broad range of anti-inflammatory effects without the side effects associated with then-current therapeutic products (PTX-353.11), demonstrating the biological benefits of Fmoc in a final drug molecule.

v. As of 1989, a POSA Would Have Been Motivated to Modify the D-Tic at Position 7 and the Oic at Position 8 in a Bradykinin Analog

22. A POSA confronted with D-Tic[13] at position 7 and Oic[14] at position 8 in the context of a peptide that otherwise appears to be a bradykinin analog would have had no reasonable expectation of success that the peptide would demonstrate bradykinin antagonism. Walensky Tr. 501:16-21, 529:25-530:22, 549:5-8. It is unequivocal that the literature did not teach or suggest: (1) the unnatural, conformationally constrained amino acids Tic or Oic in any position of a bradykinin antagonist; (2) conformationally constrained bicyclic amino acids like Tic or Oic in any position of a bradykinin antagonist; and (3) Tic or Oic to address the metabolic instability of a bradykinin antagonist. Walensky Tr. 529:25-530:22, 538:5-21, 539:5-20, 540:19-543:1; Bachovchin Tr. 184:24-185:23, 190:17-191:6, 191:17-196:4; DTX-114.5, 7.

23. Very little was known about the bradykinin receptor and its interaction with

[13] D-Tic is dextrorotatory 1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl. JTX-1 at 18:27-59.
[14] Oic is cis-endo-octahydroindol-2-ylcarbonyl. *Id.*

peptides. Walensky Tr. 495:14-17; Kyle Tr. 625:15-628:17; PTX-355.3. It was also unknown how peptide modifications made to enhance potency would impact metabolic stability, and vice versa. Walensky Tr. 549:9-550:1; PTX-250.20. And, a POSA would have understood that different hormones are individualistic—each receptor having different specificity requirements. Walensky Tr. 550:2-551:24; PTX-250.13, 15, 22. As such, design principles in one biochemical system in which Tic or Oic were tested would generally be inapplicable to an unrelated receptor. Walensky Tr. 539:21-540:18, 543:2-20, 550:2-551:24; PTX-250.13, 15, 22.

a. A POSA Would Have Had No Reasonable Expectation that D-Tic at Position 7 Would Confer Bradykinin Antagonism

24. As of 1989, it was known that D-Phe[15] at position 7 of a bradykinin analog conferred bradykinin antagonism (Walensky Tr. 535:2-536:5; Bachvochin Tr. 176:14-178:4; JTX-25.1-2 (Table 1)), as well as only certain other (e.g., small) D-aromatic amino acids (JTX-34.9). The sensitivity of antagonist activity to simple structural changes at position 7 was evidenced by abolishment of such activity by the replacement of D-Phe with Dh-Phe[16] (merely adding a single methylene group; Bachovchin Tr. 183:3-13). *Id.* at 179:25-183:13; JTX-34.5-7.

25. Although D-Tic and D-Phe share some structural similarity (e.g., differing by one methylene group at the atomic level), they differ on both the two- and three-dimensional scale. Walensky Tr. 531:19-534:19, 541:2-543:1. Bradykinin researchers recognized that although chemical structures may superficially appear similar, it is necessary to go to the atomic level to appreciate relevant differences. Kyle Tr. 644:13-648:2; PTX-360 at 36:14-16; PTX-357.10.

26. A POSA would not have been motivated to keep D-Tic at position 7 of the peptides of formula I. Walensky Tr. 530:25-531:5. Instead a POSA would have used at position

[15] D-Phe is dextrorotatory phenylalanine.

[16] Dh-Phe is dextrorotatory homo-phenylalanine. JTX-34 at 7.

7 the amino acids taught in the prior art for this position. *Id.* at 536:6-538:3; JTX-28 at 3:28-34, 4:12-45 (Table I), 18:25-29, 18:68-19:19; JTX-30 at 3:45-51, 20:13-32; JTX-38 at 3:61-67, 5:1-50 (Table I).

b. A POSA Would Have Had No Reasonable Expectation that Oic at Position 8 Would Confer the Desired Biological Activity

27. Although there was no information regarding the effect of Oic in a bradykinin antagonist, there was information as to the impact of Oic when substituted for proline in other biological systems. Walensky Tr. 543:2-20. The substitution of Oic for proline in angiotensin converting enzyme inhibitors lead to mixed results that would not have motivated a POSA to substitute Oic for proline with a reasonable expectation of success of making a potent or metabolically stable bradykinin antagonist. *Id.* at 538:22-24, 543:2-547:4; DTX-058.1, 3, 4. As such, a POSA would not have left Oic at position 8 of a peptide of the formula I, but instead would have inserted at position 8 the amino acids taught in the prior art. Walensky 547:5-548:8; JTX-28 at 3:28-34, 4:12-45 (Table I), 18:25-29, 19:20-30; JTX-38 at 3:61-67, 4:45-48.

C. Objective Indicia Support Non-Obviousness

i. Hereditary Angioedema Is Characterized by Unpredictable and Potentially Life-Threatening Acute Attacks

28. First identified in 1888, HAE is a genetic disorder characterized by attacks of localized edema (swelling) in various parts of the body. Kaplan Tr. 394:18-395:7, 399:10-400:8; PTX-180.1. HAE is caused by a mutation in the gene that produces C1 Inhibitor ("C1 INH"), a blood protein that normally functions to regulate the production of bradykinin. Kaplan Tr. 394:18-395:7. In patients with HAE, deficient or dysfunctional C1 INH levels can lead to the overproduction of bradykinin, which causes the swelling seen in an acute attack. *Id.*

29. In 1983, Plaintiffs' expert Dr. Kaplan was among the first to identify bradykinin as the molecule directly responsible for the symptoms of an acute HAE attack. *Id.* at 391:13-

392:1; PTX-191.1. By 1987, HAE was among the pathological conditions that the bradykinin antagonist literature associated with overproduction of bradykinin. *See, e.g.*, JTX-28.1, JTX-28 at 1:23-36 (referring to "hereditary angioneurotic edema."). By 1989, it was known that HAE is a bradykinin-mediated disorder.

30. An acute attack may occur without any apparent triggering event, and its symptoms may progress rapidly to a medical emergency. Kaplan Tr. 392:2-10, 402:4-20; PTX-179.2. An acute attack falls into one of three general types: (1) peripheral; (2) visceral; and (3) laryngeal. Kaplan Tr. 394:21-24. A peripheral attack involves the disfiguring and potentially disabling swelling of the hands, feet, face, or genitalia. *Id.* at 395:25-396:1, 396:25-397:24. A visceral attack involves swelling of the abdominal lining, accompanied by severe abdominal pain. *Id.* at 396:2-6. The most serious type is a laryngeal attack, in which swelling of the larynx may obstruct the airway and cause a patient to asphyxiate. *Id.* at 396:14-18, 397:25-398:21.

ii. In 1989, There Was No Safe, Effective, and Convenient Acute Treatment

31. In 1989, there was no safe, effective, and convenient treatment for an acute attack of HAE. *Id.* at 392:2-18, 401:10-402:3. At the time, treatment consisted of medical observation for worsening of symptoms while making the patient as comfortable as possible. *Id.* This may have entailed administration of intravenous fluids, pain medication, and—in case of a laryngeal attack—set-up for potential intubation or a tracheostomy. *Id.* Infusion of fresh frozen plasma derived from human donors was a treatment that was sometimes effective, although its use was controversial and not recommended to treat laryngeal attacks. *Id.* at 402:21-404:4; PTX-179.3.

32. The treatment options available in 1989 had safety risks and other drawbacks. Fresh frozen plasma was sometimes effective but potentially dangerous, because it could exacerbate the symptoms of an attack. *Id.* In the case of visceral attacks, many patients became

addicted to the pain medication (e.g., opioids) prescribed for the acute pain attendant to such attacks and/or were subjected to unnecessary surgery. *Id.* at 396:2-13.

iii. Icatibant Is a Safe, Effective, and Convenient Acute Treatment

33. After leaving Hoechst in 1998, Dr. Knolle, co-inventor of the '333 patent and former director of Hoechst's bradykinin antagonist project, approached Hoechst's successor company (Sanofi-Aventis) for a license to explore therapeutic applications of icatibant. Knolle Tr. 267:16-270:14, 302:17-304:20. At the time, Dr. Knolle was Chief Scientific Officer of Jerini AG ("Jerini"), a drug discovery and development company of no more than fifteen employees. *Id.* at 302:17-303:13. Based on his work at Hoechst, Dr. Knolle "knew and saw that [icatibant] had at least good safety and still had to find its place in the therapeutic field." *Id.* at 303:17-304:3. Sanofi granted Jerini a license, which included—for free—6.2 kg of left-over product. *Id.* at 304:21-305:1. Dr. Knolle was "very happy with the deal," particularly because the 6.2 kg of icatibant that Jerini inherited "was still stable after sitting many years there in the dark." *Id.* at 304:11-305:1. After filing for and obtaining marketing authorization in the EU for treatment of acute HAE attacks, Jerini was acquired by Shire for approximately $560 million. *Id.* at 305:17-308:9, 308:11-310:3; PTX-36.1, 36.9-11.

34. Icatibant was approved by the FDA in 2011 as a safe and effective treatment for acute attacks of HAE. Kaplan Tr. 408:15-409:6; JTX-45. Icatibant's efficacy derives from its bradykinin antagonist activity, which—unlike any other acute treatment—directly blocks bradykinin, the molecule responsible for the swelling seen in an acute attack. *Id.* at 409:10-410:22, 400:9-401:9; Andresen Tr. 801:1-25. Icatibant's safety profile is likewise intrinsic to the molecule and—unlike other acute HAE treatment—presents no risk of anaphylaxis. Kaplan Tr. at 406:15-406:19, 410:24-411:13, 412:8-13; JTX-47.1; Andresen Tr. 802:5-15.

35. Icatibant is a convenient treatment for acute attacks of HAE. Its safety profile allows for self-administration, unlike other acute treatment that requires administration by a healthcare professional. Kaplan Tr. 412:23-414:3; JTX-45.1. Icatibant's bioavailability allows it to be injected subcutaneously, unlike other acute treatment that requires intravenous infusion. Kaplan Tr. at 412:8-414:3; JTX-45.1. Unrebutted testimony by Dr. Kaplan establishes that intravenous infusion is far less convenient—even if self-administered—than subcutaneous injection, particularly for a patient in the throes of an acute attack. Kaplan Tr. 405:23-406:14, 440:10-442:13; JTX-21.3-4. Icatibant's stability allows it to be supplied as a pre-filled syringe stored at room temperature, unlike other acute treatments that require reconstitution or refrigeration. Kaplan Tr. 410:24-412:7. Icatibant met the need for safe, effective, and convenient treatment of acute HAE attacks. *Id.* at 394:6-16, 407:25-408:12, 439:1-9.

36. The clinical advantage of icatibant's safety, efficacy, and convenience is undisputed. Based on over forty years of experience treating HAE patients, Dr. Kaplan testified that faster treatment leads to better clinical outcomes, e.g., faster symptom relief. *Id.* at 414:5-415:23, 439:17-440:9; PTX-227. Because it is the fastest-administered, icatibant offers clinical benefits over other acute treatments. *Id.* at 414:5-415:23, 439:17-440:9. Fresenius decided not to call its clinical expert in rebuttal to Dr. Kaplan. *Compare* D.I. 94 at 186-88 *with* Tr. 796:2-6.

iv. Icatibant's Safety, Efficacy, and Convenience Have Made FIRAZYR a Commercial Success

37. FIRAZYR has been a commercially successful product, as evidenced by its sales, profitability, and performance compared to other acute treatments. Sales of FIRAZYR have increased every year since its launch, exceeding industry expectations and even Shire's own forecasts. Bell Tr. 652:3-656:8; PTX-081.1; PTX-082.1. There is no dispute that FIRAZYR has been profitable, generating $1.2 billion in global operating income with a roughly 74 percent

profit margin as of 2016. Bell Tr. 656:9-658:3.

38. It is undisputed that FIRAZYR has outperformed other acute HAE treatments. Hofmann Tr. 820:10-20, 821:7-13. After its first year on the market, FIRAZYR accounted for the majority of sales revenue among products indicated for acute attacks of HAE. Bell Tr. 658:4-659:5, 660:1-12; PTX-088. FIRAZYR achieved this majority share when it was Shire's only HAE product. Hofmann Tr. 820:24-821:13. Sales of FIRAZYR remain considerably higher than those of other acute treatments. Bell Tr. 658:4-659:5.

39. Icatibant's safety and efficacy allow FIRAZYR to be on the market. Bell Tr. 660:17-661:1, 661:23-663:22; Hofmann Tr. 828:4-7, 828:11-15. Moreover, icatibant is in its own therapeutic class: no other bradykinin antagonist has been found safe and effective for treating HAE, or for that matter any other indication. Hofmann Tr. 826:4-828:3.

40. The "convenience properties" of icatibant set FIRAZYR apart from other acute treatments. Because of icatibant, FIRAZYR is the only acute treatment that may be self-administered subcutaneously. *See* Hofmann Tr. 825:2-21; Kaplan Tr. 412:8-414:3, 410:24-412:7; Bell Tr. 660:17-661:1, 661:23-663:22. Third-party analysts have praised the unique properties of FIRAZYR (icatibant) as the "holy grail for acute HAE treatment" and a "treatment paradigm shift." Bell. Tr. 667:24-668:18, 663:4-667:20; JTX-13.1; PTX-155.1, 155.5-6. Unrebutted testimony by Dr. Kaplan echoes this sentiment. *See* FF ¶ 35. Documents relied on by both parties' experts affirm the importance of fast and effective treatment to physicians, patients, and healthcare payors. Bell Tr. 688:8-689:19; Hofmann Tr. 821:21-824:2; PTX-141.57; JTX-43.28, 32.

41. Fresenius failed to show that FIRAZYR's commercial success is due to factors other than the safety, efficacy, and convenience afforded by icatibant. Mr. Hofmann did not

explain how "dynamics" specific to the HAE market account for FIRAZYR's outperformance of other orphan drugs within that same market and subject to the same "dynamics." *See* Hofmann Tr. 813:5-11, 819:20-820:20. Nor did Mr. Hofmann rely on any documentary evidence that patients, physicians, or healthcare payors prefer FIRAZYR on the basis of its per-attack price.[17] *See* Hofmann Tr. 813:12-814:4; PTX-092.1. To the contrary, there is no indication in the market research that price is a primary reason cited by physicians for prescribing FIRAZYR over other acute treatments. Bell Tr. 688:8-689:19; PTX-141.57.

v. No Documents Exist to Support an Allegation that Nova Independently Identified Icatibant or Any Other Bradykinin Analog with D-Tic at Position 7 Prior to Publication by Hoechst

42. Without any corroborating documentary evidence (Burch Tr. 251:4-9), Dr. Burch testified that over twenty-five years ago, Nova independently derived the icatibant sequence having D-Tic at position 7 and Oic at position 8. *Id*. at 235:17-236:15. Dr. Burch also testified that NPC 16731[18], a different molecule than icatibant but also having D-Tic at position 7, had been synthesized by Nova "coincidentally and independently" from Hoechst's disclosure of that same sequence[19]. *Id.* at 235:2-12; JTX-9.3. Dr. Burch denies that Nova was aware of "any of Hoechst's work when Nova first identified [NPC 16731]." Burch Tr. 264:16-22, 231:19-232:2.

43. This testimony is inconsistent with Dr. Burch's own publication (*id*. at 257:16-258:23) that describes Nova's substitutions made at the 7 and 8 positions of NPC 16731 as "derived from" the Hoechst substitutions of "D-Tic 7, Oic 8" for icatibant. *Id*. at 259:11-18,

[17] Plaintiffs' economic expert Dr. Bell identified documentation suggesting that FIRAZYR's competitor Berinert has the lowest per-attack price. Bell Tr. 669:1-670:18; PTX-170.1.

[18] NPC 16731 is a compound of the formula D-Arg-Arg-Pro-Hyp-Gly-Thia-Ser-D-Tic-Tic-Arg. Burch Tr. 235:10-12, 247:1-4; Raines Tr. 350:3-7; JTX-9.3. NPC 16731 is also referred to as "peptide I" in Kyle I. JTX-9.3.

[19] Dr. Burch relies on Kyle I for this proposition, but provided conflicting testimony as to how the citation to Hoechst's application was added to Kyle I. Burch Tr. 233:9-16 *cf.* 245:1-21.

260:4-261:21. Moreover, documents demonstrate that Nova disclosed data on bradykinin analogs with D-Tic at position 7 (e.g., NPC 16731) **only after** Hoechst published the sequences of many peptides having D-Tic at position 7, including icatibant and NPC 16731. *See* FF ¶¶ 82-83; Kyle Tr. 641:9-641:24. Even Kyle I, another Burch publication, acknowledges that Nova was aware of Hoechst compounds having D-Tic at the 7 position (i.e. "peptide III"): "Although peptides I and III [had] been recently disclosed in [Hoechst's] European patent application," only "the former was discovered coincidentally and independently" in the Nova laboratories. JTX-9.3-4; Kyle Tr. 634:23-635:5.

D. The '333 Patent Is Not Unenforceable Due To Prosecution Laches

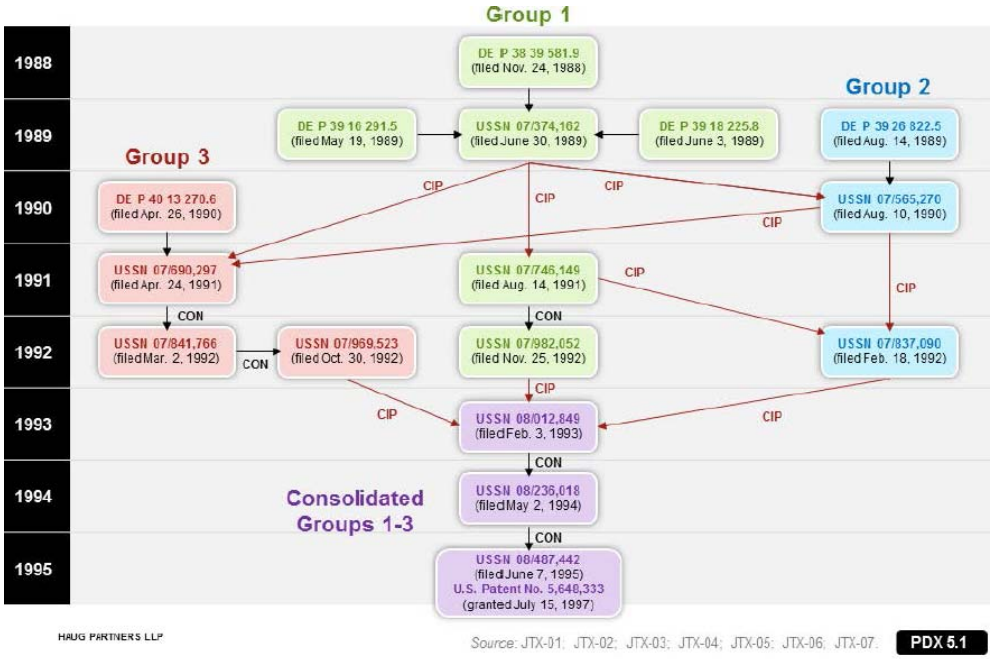
i. There Was No Unreasonable and Unexplained Delay

44. Applicants, Hoechst AG (JTX-1.2[73]; UF ¶ 7), never took any action or steps to delay the prosecution of the '333 patent. Wingefeld Tr. 720:18-721:7. Fresenius's alleged four-year delay—May 31, 1991 to June 6, 1995 (Raines Tr. 340:8-22)—was six years before the '333 patent was licensed in 2001 (Knolle Tr. 305:17-306:9; PTX-036.1, 28), and sixteen years before icatibant was FDA-approved in 2011 (UF ¶¶ 11, 12), and is unrelated to the five-year patent term extension granted under 35 U.S.C. § 156 based upon the regulatory review (JTX-2.393, 394).

45. The entire prosecution of the '333 patent (June 30, 1989 to July 15, 1997) took only eight years. Wingefeld Tr. 701:10-15; JTX-1.2. For half of that time, Fresenius's expert Dr. Raines concedes that there was no delay. Raines Tr. 357:14-358:17.

46. The USPTO never issued a warning of prosecution laches for the '333 patent, although examiners had authority to do so when appropriate. Ellis Tr. 794:1-6, 14-19.

a. The '333 Patent Contains Three Distinct Inventions and Applicants' Goal Was to Get All Filed Claims Allowed



47. The '333 patent resulted from German priority and U.S. applications of three distinct inventions (Groups 1-3). Wingefeld Tr. 702:14-703:18, 706:6-708:25, 709:10-16, 710:15-711:12; JTX-1.2[21, 30, 63]; JTX-7A.294-295; UF ¶¶ 6, 88-95, 99-112.

48. On June 30, 1989, the first U.S. application, the '162 application, was filed in Group 1. Wingefeld Tr. 701:7-13; JTX-1.2[63]; JTX-7A.294-295; UF at ¶ 6.

49. Upon the filing of the '270 application in Group 2 on August 10, 1990 and the '297 application in Group 3 on April 24, 1991 (UF ¶ 6), Groups 1-3 were prosecuted separately, but concurrently (not individually lengthening the prosecution time), until February 3, 1993. Wingefeld Tr. 708:10-25, 710:2-16; JTX-1.2[63]; JTX-7A.294-295.

50. On February 3, 1993, Groups 1-3 were consolidated into the '849 continuation-in-part ("CIP") application (UF ¶ 101), only in the U.S., to overcome OTDP rejections over the separate groups and to expedite prosecution. Wingefeld Tr. 708:10-25, 709:10-16, 710:9-14, 711:13-16, 716:22-717:21, 737:4-23; JTX-7A.7-110, 197-199.

51. The ’849 CIP application contained over 200 examples of peptides and 34 claims and was the first U.S. application containing all the subject matter of the inventions of Groups 1-3. Wingefeld Tr. 709:1-6; 734:23-735:14; JTX-7A.9, 48-109.

52. Following the ’849 CIP application, on May 2, 1994, the ’018 application was filed in the consolidated groups. Wingefeld Tr. 718:1-5. Then on June 7, 1995, the ’442 application was filed and issued as the ’333 patent. JTX-1.2[11, 21, 22, 45]; UF ¶¶ 4-5, 88.

53. Applicants’ goal and actions taken during the ’333 patent prosecution were always to get all filed claims allowed. Wingefeld Tr. 703:19-22, 704:2-8, 735:21-736:2. The ’333 patent issued with claims from all three groups. *Id.* at 705:20-23, 717:22-25.

54. Dr. Wingefeld explained that filing CIP applications, like the ’149 CIP application and the ’849 CIP application in Group 1, and the ’090 CIP application in Group 2—was common—because it allowed the applicants to add matter (like examples and data) and to add or amend claims. *Id.* at 699:12-17, 711:23-713:1. Filing continuation applications, like the ’052 application in Group 1, the ’766 application and the ’523 application in Group 3, and the ’018 application—was common—because it allowed the applicants to maintain the priority date, but continue prosecution. *Id.* at 713:2-24. Dr. Wingefeld also explained that filing a continuing application allowed prosecution to continue on, and avoided the lengthy appeal process. *Id.* at 713:25-715:3. And applicants filed applications under Rule 62 (37 C.F.R. 1.62), like the ’149 CIP, ’052, ’090 CIP, ’766, ’523, and ’018 applications, because they believed that resulted in a faster response from the USPTO. *Id.* at 726:20-727:3; JTX-4.291, 311; JTX-5A.186; JTX-6A.316, 491; JTX-7A.235. Applicants never filed a continuing application that re-filed allowed claims.

b. Prosecution of Group 1 Was Reasonable and Explained

55. The ’162 application contained 164 examples of specific peptides, *in vitro* data of

antagonist activity for 25 of those peptides, and 6 genus claims (Dr. Raines agreed). JTX-6A.10, 27-28, 31-59; UF ¶ 96; Raines Tr. 370:15-19. Dr. Raines further testified that genus Claim 1 of the '162 application covered millions of compounds. Raines Tr. 368:5-13; JTX-6A.121-124.

56. On August 17, 1990, the first office action in the '162 application rejected **genus Claims 1-6**, among other rejections, for lack of utility (35 U.S.C. § 101). JTX-6A.152-159. The rejection stated "[t]he specification does not support the asserted utility of the claimed method of treating the broad pathological disorders." JTX-6A.154. Additionally, it seemed to request *in vivo* data to support the utility of the claimed compounds. JTX-6A.154-155.

1. *In Vitro* Data Was Sufficient Under Utility Guidelines

57. On February 19, 1991, applicants responded with an amendment and remarks, including deleting claims 1-4, amending claims 5-6, and adding claims 7-13. JTX-6A.221-242. Newly-added claim 13 was to icatibant. Raines Tr. 372:11-373:1; JTX-6A.229.

58. Applicants argued that the *in vitro* data for the 25 peptides in the specification "established sufficient statutory utility for the compounds of the instant invention as set forth in M.P.E.P. § 608.01(p)." Wingefeld Tr. 723:8-21; JTX-6A.233. Applicants pointed to the utility guidelines that permitted: "[p]roof of utility under [M.P.E.P. § 608.01(p)] may be established by clinical **or** *in vivo* **or** *in vitro* data, **or** combinations . . ." JTX-6A.233 (emphasis added); Ellis Tr. 794:7-10; PTX-072.2. Dr. Wingefeld explained that it was uncommon to include *in vivo* data because it was not necessary according to the utility guidelines. Wingefeld Tr. 724:2-725:1.

2. Wirth (1991) Related to One Species Only, Icatibant

59. Wirth (1991), *in vivo* data that applicants had—and which Dr. Raines agreed related to icatibant only, not the other compounds in genus Claims 1-6—was not responsive. Raines Tr. 354:1-8, 360:14-361:2, 369:18-370:19; Wirth Tr. 454:6-18; DTX-050.

60. Dr. Raines contends that Wirth (1991) "**could have been** responsive," but admits

that he could not read the examiner's mind, did not know what the M.P.E.P. was, never asked if the utility rejection was proper, and never reviewed the utility guidelines relied on by applicants. Raines Tr. 355:9-20, 357:11-13, 365:10-22, 366:9-367:12, 370:4-10 (emphasis added); PTX-072.

3. Icatibant Was Not Even Rejected for Lack of Utility

61. A May 31, 1991 final office action rejected all claims on multiple grounds. JTX-6A.247-255. Genus claims 5-12 were rejected for lack of utility, but claim 13 to the icatibant species was not. JTX-6A.248-250. The examiner stated that "[a]pplicants have not provided the requisite evidence to prove that applicants' claimed peptide(s) would be effective in the alleged claimed method of treating the different pathological states." JTX-6A.248. Dr. Raines agreed that icatibant was not rejected for lack of utility, but still asserted that Wirth (1991) (only to icatibant) "could have been responsive." Raines Tr. 375:6-14; JTX-6A.248; FF ¶¶ 59, 60.

4. Applicants Added *In Vitro* Data For 46 Peptides

62. Only 2.5 months later, on August 14, 1991, applicants responded by filing the '149 CIP application, which added peptide examples 165-195, additional *in vitro* data for 46 specific peptides, and claims 14-17. Wingefeld Tr. 712:15-713:1, 725:2-726:6; JTX-6A.316-331.

63. Applicants added *in vitro* data in the '149 CIP application to underline the utility of the entire invention. Wingefeld Tr. 727:4-11. Dr. Wingefeld explained that it would have been difficult to obtain *in vivo* data for all 195 peptide examples. *Id.* at 726:7-19.

5. The Examiner Was Already Aware of Wirth (1991)

64. A July 1, 1992 office action issued in the '149 CIP application. JTX-6A.468-479.

65. The same Wirth (1991) publication that Dr. Raines asserts "could have been responsive" to the utility rejection became part of the record and was cited by the examiner as the basis to reject claims 5-17 under 35 U.S.C. § 102(f) for claiming an identical compound and

method. Raines 376:17-377:20; Wingefeld Tr. 728:1-19; JTX-6A.476.

66. Only genus claims 5 and 6 were rejected for lack of utility—"[t]he specification fails to factually show that the **claimed peptides used in the claimed method would treat all/or any of the pathological states**." JTX-6A.470 (emphasis added); FF ¶ 55. A restriction requirement to icatibant was withdrawn and all species were being examined. JTX-6A.153, 469.

67. On November 25, 1992, applicants responded to the July 1, 1992 office action by filing the '052 application because they were considering how to respond to the OTDP rejections pending over the three groups (JTX-4.300, 301; JTX-5A.204; JTX-6A.474, 475). Wingefeld Tr. 713:2-6, 728:20-729:6; JTX-6A.491-496.

6. The '849 CIP Application Overcame OTDP Rejections

68. The '849 CIP application, filed less than three months after the '052 application and before an office action issued, overcame the OTDP rejections. JTX-6A.497; FF ¶¶ 50, 67.

69. On May 3, 1993, applicants submitted an information disclosure statement that included Wirth (1991), which the examiner considered on November 1, 1993. JTX-7A.209-214.

70. A November 3, 1993 office action rejected all genus and species claims 1-34 for lack of utility, among other rejections, despite the examiner having again considered Wirth (1991). JTX-7A.217-232. Groups 2 and 3 had not been previously rejected for lack of utility.

71. After filing the '018 application, on December 6, 1994, the USPTO issued an office action still rejecting all of the claims 1-34 for lack of utility, among other reasons. Wingefeld Tr. 737:24-738:13; JTX-7A.246-260; FF ¶ 52.

7. In January 1995, Utility Guidelines Were Updated

72. In January 1995, Updated Utility Guidelines were noticed—to "address issues that may arise during examination of applications claiming protection for inventions in the field of biotechnology and human therapy"—in response to an uproar in the biotechnology industry

over the inconsistency in utility rejections in the newly-formed USPTO biotechnology group. Ellis Tr. 794:20-795:17; PTX-073.2. The Updated Utility Guidelines made clear that applicants can rebut a lack of utility "by amending the claims, by providing reasoning or arguments, or by providing evidence." PTX-073.3. Examiners were reminded "that they must treat as true credible statements" made in the specification or in a declaration. PTX-073.3.

73. Applicants conducted an examiner interview on May 30, 1995 (JTX-7A.261, 292), which was not common at the time. Wingefeld Tr. 718:6-719:25.

8. June 6, 1995 Response (End of Alleged Delay)

74. One week after the interview, on June 6, 1995, applicants filed an amendment and remarks in the '018 application in response to all rejections. Wingefeld Tr. 738:20-739:2; JTX-7A.263-392. Applicants cancelled claims 1-34 and added claims 35-67. JTX-7A.263-292.

75. Applicants maintained that the *in vitro* data in the specification (for over 70 peptides) was sufficient to establish utility. Wingefeld Tr. 739:3-10; JTX-7A.42-43, 83-84, 299. With over 200 examples in the specification, applicants did not believe that *in vivo* data for just icatibant (in Wirth (1991)) would overcome the utility rejection. Wingefeld Tr. 765:14-766:1.

9. Applicants Complied with the 1995 Utility Guidelines

76. In compliance with the Updated Utility Guidelines—which reminded examiners to treat declarations as credible—applicants submitted a declaration of inventor Schölkens. *Id.* at 739:22-740:17; Ellis Tr. 794:1-2, 11-13; JTX-7A.299, 327-331; PTX-073.3. Dr. Raines admitted that he had not read and was not familiar with the Updated Utility Guidelines despite the applicants' citation to it. Raines Tr. 379:21-381:2; JTX-7A.299; PTX-073.

10. More than Wirth (1991) Overcame Utility Rejection

77. The Schölkens declaration relied on Wirth (1991) and a Wirth 1993 publication, which studied the effects of only icatibant. Wingefeld Tr. 741:8-742:5; JTX-7A.329-330.

78. In further support of utility, applicants also submitted seven other publications from 1992-1994 (five from 1993-1994) that could not have been submitted earlier and attested to utility in treating a variety of pathological states. Wingefeld Tr. 740:18-741:7; JTX-7A.301-302.

79. Dr. Raines agreed that it was not the Wirth (1991) publication alone that resulted in the utility rejection being withdrawn. Raines Tr. 377:21-379:20.

11. All Claims Were Still Rejected After the Alleged Delay

80. Even after the June 6, 1995 response, applicants received a final office action on November 6, 1995. Although the utility rejection was withdrawn, all pending claims 35-67 were still rejected on multiple grounds. Wingefeld Tr. 739:3-21; JTX-7A.427-437.

ii. There Was No Prejudice

a. There Is No Evidence that Nova Invested in NPC 16731 During the Alleged Delay and Was Adversely Affected

81. Dr. Burch left Nova in the Fall of 1991 and has no personal knowledge or access to Nova information after that time, so he cannot provide evidence of any "investment" in NPC 16731[20] during the alleged delay. Burch Tr. 210:21-24, 242:14-243:14. Dr. Burch had no documentary evidence and was providing only his best guess to assert that Nova invested in NPC 16731. Nor did he have documentary evidence that Nova invested in any other compound claimed by the '333 patent during the alleged delay. *Id.* at 251:1-16.

82. Farmer and Kyle I are the only documents offered by Fresenius about Nova's work with NPC 16731. *Id.* at 262:20-25. The work in Farmer was completed and submitted to the journal by October 26, 1990—before the alleged delay. *Id.* at 249:22-25; Kyle Tr. 632:5-15; JTX-41.3. The work in Kyle I, where NPC 16731 was identified as Peptide I, was completed and submitted to the journal by December 10, 1990—also before the alleged delay. Burch Tr.

[20] NPC 16731 is claimed in unasserted claim 12 of the '333 patent in Group 1(not in asserted claim 14 or in Groups 2-3). Raines Tr. 315:23-316:3, 351:4-7; FF ¶ 42 n.18.

234:13-17, 244:7-22; Kyle Tr. 633:10-22; JTX-9.3, 5. Dr. Raines also had no information concerning Nova, other than Farmer and Kyle I. Raines Tr. 381:6-11.

83. After Hoechst learned that Nova had made two presentations in 1990 concerning NPC 16731, in February 1991, it advised Nova that NPC 16731 was first disclosed in Hoechst's European Patent Application 89121498.3 (upon filing in November 1989[21] and publication on May 30, 1990). Wingefeld Tr. 750:10-751:18; PTX-058; Burch Tr. 246:13-19, 247:1-247:10, 248:8-249:4; Kyle Tr. 638:17-24, 641:3-24; PTX-356.1, 38; PTX-357T.2; PTX-357.1, 17. Nova responded in March 1991 by two separate letters apologizing for failing to give credit to Hoechst for NPC 16731. Wingefeld Tr. 751:19-752:25; PTX-059; PTX-060. Nova made those apologies, despite Nova's earlier claim in Kyle I that Nova had "discovered coincidentally and independently" NPC 16731. JTX-9.3, 4; PTX-059; PTX-060. Nova's apology letters made no mention of its supposed independent discovery of NPC 16731. PTX-059; PTX-060. The letters with Nova and Nova's apologies did not make Hoechst take any action to delay the prosecution of the '333 patent. Wingefeld Tr. 753:1-4. Applicants even disclosed Kyle I to the USPTO pointing out Nova's claim of independent discovery and Hoechst's earlier European Patent Application 89121498.3 disclosure; the examiner considered Kyle I. JTX-6A.244, 256-257.

84. Nova's peptide bradykinin antagonists had significantly shorter duration of action than icatibant. Wirth Tr. 462:13-463:9, 463:25-464:10; PTX-061T.7. Nova made it known that it had pulled out of the peptide bradykinin antagonist field because its compounds were not superior. Wirth Tr. 458:12-459:5; PTX-062T.3. Nova's goal was to find a non-peptide bradykinin antagonist. Wirth Tr. 459:6-23; PTX-062T.5. NPC 16731 was never a product and never a clinical lead compound. Burch Tr. 249:5-6, 250:4-8. As of the Fall of 1991, Nova had no

[21] NPC 16731 was also disclosed in the '162 application upon filing on June 30, 1989. JTX-6A.6, 38.

ongoing bradykinin antagonist clinical studies at all. *Id.* at 250:9-12.

85. Because Nova had financial problems, it focused its priorities on its commercially attractive leumedins program. *Id.* at 250:19-21, 254:16-255:18. Nova's change in priorities was not related to Hoechst. *Id.* at 255:8-18. Nothing that Hoechst did impacted Nova's bradykinin antagonist program. Kyle Tr. 619:7-23.

b. Fresenius Was Not Working on Icatibant During the Alleged Period of Delay and Cannot Have Intervening Rights

86. Fresenius did not invest in, work on, or use icatibant[22] during the alleged period of delay—Fresenius did not even begin its icatibant project until 2014—nineteen years after the end of the alleged delay. Dron Tr. 693:12-14, 694:13-695:8, 695:21-696:21; PTX-277.1; PTX-294.

87. Fresenius was not deterred from taking any action. Because icatibant is a new chemical entity, Fresenius could not have filed its ANDA any earlier than it did. UF ¶¶ 13, 23.

III. PLAINTIFFS' PROPOSED CONCLUSIONS OF LAW

A. The Person of Ordinary Skill in the Art in the Context of the '333 Patent

88. POSA "is an objective legal construct presumed to think along conventional lines without undertaking to innovate . . . ." *See Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) (citing *Std. Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985)). A POSA in the context of the '333 patent is a person who has at least a Ph.D. in organic chemistry, medicinal chemistry, pharmacology, or a similar field, and has a working knowledge of the chemistry and biochemistry of bradykinin or other peptides for the purposes of drug development. (FF ¶ 2); *see Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007) (quoting *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983)(identifying parameters for determination of a POSA)).

[22] Asserted claim 14 to icatibant is part of Group I. Raines Tr. 315:23-316:3, 328:10-13.

B. Properly Construed, the Peptide of Claim 14 Is a Bradykinin Antagonist

89. "Claim construction requires a determination as to how a [POSA] would understand a claim term 'in the context of the entire patent, including the specification.'" *Trs. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1362 (Fed. Cir. 2016) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc)). The specification is the primary basis for construing claims. *Trs. of Columbia Univ.*, 811 F.3d at 1362. The scope of the claims cannot be broader than the invention set forth in the specification. *On Demand Mach. Corp. v. Ingram Indus. Inc.*, 442 F.3d 1331, 1340 (Fed. Cir. 2006); *see also Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001); *Ruckus Wireless, Inc. v. Innovative Wireless Sols., LLC*, 824 F.3d 999, 1003 (Fed. Cir. 2016) (using the title as a guide for claim construction).

90. Every example and peptide in the '333 patent is a bradykinin antagonist; no other biological activity is ever mentioned. FF ¶ 3. Because the scope of the claims cannot be broader than the disclosed invention (i.e., bradykinin antagonists) (*see On Demand*, 442 F.3d at 1340), in light of the specification of the '333 patent a POSA would have construed claim 14 as a peptide of the formula H-D-Arg-Arg-Pro-Hyp-Gly-Thia-Ser-D-Tic-Oic-Arg-OH, or a physiologically tolerable salt of said peptide with bradykinin antagonist activity. FF ¶¶ 1, 3.

91. The invention date is when conception occurs and there is "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 967 (Fed. Cir. 2014) (quoting *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994)). Because the peptide of claim 14 of the '333 patent was determined to be a bradykinin antagonist on January 19, 1989 (FF ¶ 1), that is the date of invention of claim 14.

C. Invalidity Must Be Proven by Clear and Convincing Evidence

92. Every issued patent claim is presumed valid. 35 U.S.C. § 282. To overcome this presumption, a party must prove invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011). To prevail on its OTDP defense, Fresenius had to prove by clear and convincing evidence that claim 14 of the '333 patent is an obvious variant of claim 1 of the '7,803 patent in view of the prior art. Fresenius did not meet this burden.

i. Fresenius Has Failed to Prove that Claim 14 of the '333 Patent Is Invalid for Obviousness-type Double Patenting

93. OTDP is a judicially created doctrine that precludes claims in a second patent that are not patentably distinct from claims in a first patent. *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1297 (Fed. Cir. 2012). The ultimate determination of OTDP is a question of law premised on underlying findings of fact. *Otsuka Pharm.*, 678 F.3d at 1290; *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368, 1376 (Fed. Cir. 2012).

94. OTDP employs a two-step test: "(1) construction of the claims in the earlier patent and the claim in the later patent to identify any differences, and (2) determination of whether the differences in subject matter between the claims render the claims patentably distinct." *Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1361 (Fed. Cir. 2009); *see also Otsuka Pharm.*, 678 F.3d at 1297–300.

95. Once the differences in the claims are established, it must be decided whether such differences render the claims patentably distinct in light of the prior art (*see Amgen Inc.*, 580 F.3d at 1361–62), but those differences cannot be considered in isolation such that the claims must be considered as a whole (*see Eli Lilly*, 689 F.3d at 1377). Whether the differences in the subject matter between the claims renders the claims patentably distinct in an OTDP inquiry "is analogous to an obviousness analysis under 35 U.S.C. § 103," *Amgen Inc.*, 580 F.3d

at 1361, "except that the patent principally underlying the double patenting rejection is not considered prior art." *Id.* (quoting *In re Longi*, 759 F.2d 887, 892 n.4 (Fed. Cir. 1985)).

96. "In the context of claimed chemical compounds, an analysis of [OTDP]—like an analysis under § 103—entails determining, *inter alia*, whether one of ordinary skill in the art would have had reason or motivation to modify the earlier claimed compound to make the compound of the asserted claim with a reasonable expectation of success. There is no other way to consider the obviousness of compound B over compound A without considering whether one of ordinary skill would have had reason to modify A to make B." *Otsuka Pharm.*, 678 F.3d at 1298. While the compounds being compared "may have . . . the same general function, changes in the structure of the compounds can have significant effects on their function within the body," rendering the modification nonobvious for OTDP purposes. *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 803 F. Supp. 2d 409, 450–51 (E.D. Va. 2011).

a. A POSA Would Have Understood the Peptides of Formula I of Claim 1 of the '7,803 Patent as Having N-Terminal Modifications that Are Permanent and Integral Components of the Final Claimed Peptides

97. In this case, the first step of the two-step OTDP analysis includes the construction of claim 1 of the '7,803 patent. *See Amgen Inc.*, 580 F.3d at 1361 (Fed. Cir. 2009). Based upon the plain language of the claim, a POSA would have understood the "peptides of formula I" as having a "Z" group, such as Fmoc, that is an integral and necessary component of the final claimed peptide, not to be removed. FF ¶¶ 5-7. A POSA would have known Fmoc could be used in ways other than as a transient protecting group during peptide synthesis. FF ¶ 21. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 302 (Fed. Cir. 1985) (finding that even though "technically not prior art," a reference was "indicative of what was generally known during the relevant time frame to persons of ordinary skill in the [relevant] art"); *see also In re*

Farrenkopf, 713 F.2d 714, 719–20 (Fed. Cir. 1983). Also based upon the plain language of claim 1, a POSA would have construed the "P" group as being one of seven options as expressly listed in the claim, with no one option preferred over another. FF ¶ 8.

98. In an OTDP analysis the specification of an earlier-expiring patent may be considered to determine "whether a claim 'merely define[s] an obvious variation of what is earlier disclosed and claimed,' 'to learn the meaning of [claim] terms,' and to 'interpret[] the coverage of [a] claim.'" *Sun Pharm. Indus. v. Eli Lilly & Co.*, 611 F.3d 1381, 1387 (Fed. Cir. 2010) (citing *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d 1371, 1378 (Fed. Cir. 2008)); *see also Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, No. 08-335-GMS, 2011 WL 3236037, at *2 (D. Del. July 28, 2011) (noting that the specification of the earlier-expiring patent may serve as a guide in construing the claims of that patent); *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 518 F.3d 1353, 1363 (Fed. Cir. 2008)) (stating that nothing prevents the court from "looking to the specification [of the OTDP reference] to determine the proper scope of the claim[]"). A court must not close its eyes to the specification of the OTDP reference entirely, and may consider embodiments therein to discern whether what is later claimed is an obvious variant. *In re Hitachi Metals, Ltd.*, 603 F. App'x 976, 979 (Fed. Cir. 2015) (citation omitted).

99. The record makes clear that two terms in claim 1 of the '7,803 patent are in dispute: the "Z" group and the "P" group of a peptide of the formula I. FF ¶¶ 5, 8. In view of this dispute, the specification of this OTDP reference patent must be considered when interpreting such terms or determining what constitutes an obvious variant. *Sun Pharm. Indus.*, 611 F.3d at 1387. It is unrebutted (FF ¶ 10 n.9) and unequivocal that the '7,803 patent specification is consistent with the language of claim 1 (FF ¶¶ 5-7, 9-12) and demonstrates that the peptides of formula I are peptides with a Z group, which is a N-terminal modification that is an integral and

permanent component of the final and claimed peptide product that is not to be removed. *Id.* It is also unrebutted (FF ¶ 10 n.9) and unequivocal that, consistent again with the language of claim 1, the '7,803 patent's specification makes clear that the "P" group is any one of seven choices listed in the claim, with no one option prioritized over another (FF ¶ 8).

b. Fresenius Has Failed to Establish that a POSA Would Have Been Motivated to Modify the Peptides of Claim 1 of the '7,803 Patent to Result in the Peptide of Claim 14 of the '333 Patent

100. In this case, the second step of the two-step OTDP analysis requires the determination of whether the differences in subject matter between claim 14 of the '333 patent and claim 1 of the '7,803 patent render the claims patentably distinct in light of the prior art. *See Amgen Inc.*, 580 F.3d at 1361–62. The peptide of claim 14 of the '333 patent differs substantially from the peptides of claim 1 of the '7,803 patent in that the peptides of the '7,803 patent contain a permanent N-terminal modification not present on the peptide of claim 14. FF ¶¶ 3-7.

101. Moreover, a POSA viewing the peptides of claim 1 of the '7,803 patent in the context of the prior art would have had examples and reasons why an N-terminal modification on a peptide, including on a bradykinin antagonist, were biologically beneficial and therefore should not be removed. FF ¶¶ 14-20. Accordingly, as of 1989 a POSA would not have been motivated to remove the N-terminal modification from the peptides of formula I of claim 1 of the '7,803 patent.

102. Furthermore, the differences between claim 1 of the '7,803 patent and claim 14 of the '333 patent (e.g., the Z group such as Fmoc) cannot be considered in isolation, but rather the claims must be considered as a whole. *See Eli Lilly*, 689 F.3d at 1377. As of 1989, Tic and Oic had never been used in (FF ¶¶ 22, 27) and were substantially different from any amino acids incorporated into bradykinin antagonists (FF ¶¶ 22-27). As such, Fresenius has not proven by clear and convincing evidence that as of 1989 a POSA would have (1) known that D-Arg-Arg-

Pro-Hyp-Gly-Thia-Ser-D-Tic-Oic-Arg-OH, with or without an N-terminal modification, has bradykinin antagonist activity just by looking at the amino acid sequence and (2) left D-Tic and Oic at their respective positions in light of the bradykinin literature. A POSA would have been motivated to remove Tic and Oic from the peptides of formula I of the '7,803 patent and replace them with the amino acids recommended by the prior art for positions 7 and 8 of a bradykinin antagonist (FF ¶¶ 26-27), leading away from the peptide of claim 14 of the '333 patent.

103. Fresenius has not proven by clear and convincing evidence that claim 14 of the '333 patent is an obvious variant of claim 1 of the '7,803 patent. To the contrary, the evidence shows that claim 14 of the '333 patent and claim 1 of the '7,803 patent are patentably distinct.

D. Objective Indicia Further Support Non-Obviousness

104. "[I]n determining what would have been obvious to one of ordinary skill in the art at the time of invention, the use of hindsight is not permitted." *In re Alfuzosin Hydrochloride Patent Litig.*, No. 08-1941-GMS, 2010 WL 1956287, at *3 (D. Del. May 14, 2010). "The objective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016). Objective indicia serve no less an important role here, where OTDP relies on what would have been "obvious" to a POSA at the time of icatibant's invention. *See UCB, Inc. v. Accord Healthcare, Inc.*, 201 F. Supp. 3d 491, 536–40 (D. Del. 2016).

105. Objective indicia are considered in rebuttal to OTDP, whether or not the reference patent was publicly available at the time of invention. *Eli Lilly*, 689 F.3d at 1373–74, 1381.

106. The Federal Circuit has held that "the structure of a claimed compound and its properties" are "inseparable" considerations in the obviousness analysis. *Genetics Inst., LLC v. Novartis Vaccines and Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011); *see also In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). "[E]very property of a claimed compound need not

be fully recognized as of the filing date of the patent application to be relevant to nonobviousness." *Genetics Inst., LLC*, 655 F.3d at 1307.

i. Icatibant Satisfied a Long-Felt Need

107. Evidence of a long-felt but unmet need may support a finding of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Long-felt need is assessed at the time of invention and has been found met where a patented compound treats a condition that was "recognized as a serious disease," for which "existing treatments were inadequate." *See Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009).

108. In 1989, HAE was a known, potentially life-threatening condition, and treatment options for an acute attack were inadequate. FF ¶¶ 28-32. Icatibant satisfied the need for a safe, effective, and convenient treatment for acute HAE attacks. FF ¶¶ 33-36.

ii. Icatibant Is a Commercial Success

109. "The commercial response to an invention is significant to determinations of obviousness, and is entitled to fair weight." *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988). Commercial success has been found where a patented compound achieves "significant sales in a relevant market." *UCB, Inc.*, 201 F. Supp. 3d at 539-40; *see also Pfizer v. Mylan Pharm. Inc.*, 71 F. Supp. 3d 458, 476 (D. Del. 2014).

110. FIRAZYR is a commercial success, as evidenced by its sales, profitability, and share of the acute HAE market. FF ¶¶ 37-38. FIRAZYR's commercial success is due to the safety, efficacy, and convenience afforded by the properties of icatibant. FF ¶¶ 39-41.

iii. There Has Been No Showing of Near-Simultaneous Invention

111. "In some rare instances, the secondary consideration of simultaneous invention might also supply 'indicia of 'obviousness.'" *Geo M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010) (citations omitted). This case is not one such "rare

instance." Without more, Dr. Burch's uncorroborated twenty-five years old recollection that Nova developed icatibant (FF ¶ 42) cannot support an allegation of near-simultaneous invention.

112. Moreover, where a distinct compound is alleged to be a near-simultaneous invention of the asserted compound, this evidence should be disregarded. *See Endo Pharm. Inc. v. Amneal Pharm., LLC*, 224 F. Supp. 3d 368, 381 (D. Del. 2016). Because NPC 16731 and icatibant are two different peptides (FF ¶ 42), NPC 16731 cannot demonstrate near-simultaneous invention. Plus, "[t]he tendency of simultaneous invention to weigh in favor of obviousness" is "negated if the purported simultaneous invention was not made independently of the claimed invention." *Trs. of Columbia Univ. v. Illumina, Inc.*, 620 F. App'x 916, 930 (Fed. Cir. 2015). Here, because NPC 16731 was "derived from" the sequence of icatibant FF ¶ 43, NPC 16731 does not support near-simultaneous invention. Finally, where evidence of near-simultaneous invention comes after the first invention has been publicized, the evidence is **irrelevant**. *See Eli Lilly Co. v. Teva Pharms.*, No. IP 02-0512-C-B/S, 2004 WL 1724632 at n.23 (S.D. Ind. July 29, 2004). Because Nova's disclosure of NPC 16731 came after the publication of icatibant, it cannot provide a basis for near-simultaneous invention. FF ¶ 43, 82-83. This point is reinforced by documentary evidence showing that Nova was aware of Hoechst's work before it submitted data on NPC 16731. FF ¶ 43.

E. There Is No Clear and Convincing Evidence of Prosecution Laches

113. In view of recent Supreme Court case law and 35 U.S.C. § 282(b), laches—including prosecution laches, we submit—is no longer a defense. *See SCA Hygiene Prods. Aktiebolag v. First Quality Baby Prods., LLC*, 137 S. Ct. 954, 967 (2017) (concluding that laches was not a defense where the patentee filed suit in accordance with statute); *see also Pregis Corp. v. Kappos*, 700 F.3d 1348, 1360 (Fed. Cir. 2012) (noting that the list of statutory defenses "reflects the deliberate judgment of Congress that not every error during prosecution should

provide a[n infringement] defense"). All relevant laws and rules were followed during the '333 patent's prosecution, so courts cannot engraft a defense that has no basis in any statute or rule.

114. If the Court finds that prosecution laches remains a viable defense, the doctrine "'may render a patent unenforceable when it has issued only after an unreasonable and unexplained delay in prosecution' that constitutes an egregious misuse of the statutory patent system under the totality of the circumstances." *Cancer Research Tech. Ltd. v. Barr Labs., Inc.*, 625 F.3d 724, 728 (Fed. Cir. 2010) ("*Cancer Research II*") (quoting *Symbol Techs., Inc. v. Lemelson Med., Educ. & Research Found., LP*, 422 F.3d 1378, 1385–86 (Fed. Cir. 2005) ("*Symbol IV*")). "Egregious misuse means a 'pattern of unjustifiably delayed prosecution' designed to extend the term of the patent." *Novozymes A/S v. Genencor Int'l, Inc.*, 446 F. Supp. 2d 297, 333 (D. Del. 2006) (quoting *Symbol IV*, 422 F.3d at 1385-86).

115. The "unreasonable and unexplained delay" requirement "includes a finding of prejudice, as does any laches defense" and in order to establish prejudice, "an accused infringer must show evidence of intervening rights, *i.e.*, that either the accused infringer or others invested in, worked on, or used the claimed technology **during the period of delay**." *Cancer Research II*, 625 F.3d at 729 (emphasis added). There must be "a finding that the **applicant's delay in prosecution adversely affected others** working in the same field." *Id.* (emphasis added).

116. A defendant must prove prosecution laches by clear and convincing evidence. *Medtronic, Inc. v. Boston Sci. Corp.*, 777 F. Supp. 2d 750, 782–83 (D. Del. 2011).

i. There Was No Unreasonable and Unexplained Delay in the '333 Patent Prosecution that Constitutes an Egregious Misuse of the Statutory Patent System Under the Totality of the Circumstances

117. "There are legitimate grounds for refiling a patent application which should not normally be grounds for a holding of laches, and the doctrine should be used sparingly lest statutory provisions be unjustifiably vitiated." *Symbol IV*, 422 F.3d at 1385, *amended on reh'g in*

part by, 429 F.3d 1051 (Fed. Cir. 2005). "Commonly, and justifiably, one might refile an application to add subject matter in order to attempt to support broader claims as the development of the invention progresses. . . ." *Id.* Moreover, an application may be refiled for any reason, "provided that such refiling is not unduly successive or repetitive." *Id.*

118. The filing of multiple continuing applications is not *per se* unreasonable. *Novozymes*, 446 F. Supp. 2d at 334 (finding based upon a "series of continuations and divisions," that the "Defendants have failed to show anything unreasonable about that familiar course of prosecution"). "It is not enough for a defendant to show . . . refiling of rejected claims or the use of continuation applications to add new subject matter." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 529 F. Supp. 2d 106, 137 (D. Mass. 2007).

119. An applicant's decision to file a continuation application instead of appealing a rejection does not constitute an unreasonable or unexplained delay in prosecution. *Ariad Pharm.*, 529 F. Supp. 2d at 137–38; *see Regents of the Univ. of Cal. v. Monsanto Co.*, No. 04-0634-PJH, 2005 WL 3454107, at *25 (N.D. Cal. Dec. 16, 2005).

120. Prosecution laches, applying only to egregious cases, has not been found for any alleged delay as short as what Fresenius alleges here. *E.g.*, *Symbol Techs., Inc. v. Lemelson Med., Educ. & Research Found., LP*, 301 F. Supp. 2d 1147, 1155 (D. Nev. 2004), *aff'd*, *Symbol IV*, 422 F.3d at 1386 (finding that 18- to 39-year prosecutions were unreasonable and unexplained, including the refiling of eighteen applications with previously-allowed claims). Multiple courts have declined to find prosecution laches for prosecution longer than that of the '333 patent. *See, e.g.*, *Medtronic*, 777 F. Supp. 2d at 782–83 (finding no unreasonable and unexplained delay in 14-year prosecution); *Novozymes*, 446 F. Supp. 2d at 334 (same for 10-year prosecution).

121. Whether "the prosecution history of plaintiff's patents was typical of patents in

that field or patents generally" is a relevant consideration in assessing unreasonable delay. *Regents*, 2005 WL 3454107, at *24.

122. Filing the '442 patent application or June 6, 1995 office action response immediately prior to the enactment of GATT (UF ¶¶ 85, 86) is not unreasonable or unexplained, and not relevant. *Ariad Pharm.*, 529 F. Supp. 2d at 139 ("[The patentee's] desire to obtain the maximum term for its patent grant, particularly when the rules were being changed, is neither unreasonable nor unexplained."); FF ¶ 52, 74.

123. "[T]he PTO has the authority to reject patent applications for patents that would be unenforceable" for prosecution laches. *In re Bogese*, 303 F.3d 1362, 1367 (Fed. Cir. 2002). (PTO rejected claims for prosecution laches in 1995). That the PTO did not do so during the prosecution of the '333 patent weighs against a finding of prosecution laches. FF ¶¶ 46.

124. The prosecution of the '333 patent, including the filing of continuing applications, was not unreasonable, unduly successive, or repetitive. FF ¶¶ 44-80.

125. The prosecution of the '333 patent was explained and was typical of patent applications filed in the biotechnology field at the USPTO at the time. FF ¶¶ 44-80.

126. Prosecution laches does not apply here because an 8-year prosecution, with an alleged delay of less than four years, is not unreasonable. FF ¶¶ 44-54, 62, 68.

ii. Fresenius Failed to Show Prejudice During and by the Alleged Delay

127. In order to establish prejudice, Fresenius must show that the alleged delay in prosecution "adversely affected" the party with intervening rights. *Cancer Research II*, 625 F.3d at 729-732 (rejecting argument that "the public was inherently prejudiced by [patentee's] delay" and recognizing "intervening adverse rights [during the period of delay] as a requirement"); *Gen-Probe Inc. v. Vysis, Inc.*, No. 99-cv-2668, 2002 WL 34413199, at *119 (S.D. Cal. Aug. 5, 2002) ("Prosecution laches thus apply where the patent applicant delays deliberately, unreasonably and

without excuse the issuance of his patent **so as to prejudice the intervening rights of another party**.") (emphasis added); *see Chiron Corp. v. Genentech, Inc.*, 268 F. Supp. 2d 1139, 1144 (E.D. Cal. 2002) (A defendant must show "that there is a nexus between [the applicants'] delay in prosecuting the [patent-in-suit] and the alleged prejudice.").

128. In order to show that a party was "adversely affected," Fresenius must show that the holder of intervening rights would have either done something differently or experienced a change in economic position as a result of the alleged delay in issuance of the patent-in-suit. *Cancer Research II*, 625 F.3d at 731 ("There has been no evidence presented that anyone was deterred from entering the market for temozolomide because Cancer Research's patent issued in 1993 rather than several years earlier"); *Ormco Corp. v. Align Tech., Inc.*, 647 F. Supp. 2d 1200, 1207 (C.D. Cal. 2009) (finding "an insufficient showing of prejudice to Align['s intervening rights] to support a finding of laches [sic]" because "Align has failed to set forth evidence indicating that Align would have done anything differently if it had been faced with the asserted claims of the '444 patent sooner."); *Chiron Corp.*, 268 F. Supp. 2d at 1145 ("The change in the defendant's economic position 'must be because of and as a result of the delay, not simply a business decision to capitalize on a market opportunity.'").

129. Prosecution laches should not apply when the content of the patent-in-suit is published prior to the patent issuance because applicants did not take steps to limit public awareness, as is the case here. *Regents*, 2005 WL 3454107, at *24; FF ¶ 83.

130. "[W]hen one considers the public interest, the public has benefitted by the fact that" a patentee develops and markets a drug induced by the protection of its patent. *Cancer Research II*, 625 F.3d at 732. A patentee "should not lose [patent] protection because its patent issuance was delayed under circumstances where no one suffered prejudice." *Id.*

131. Fresenius did not prove that Nova was prejudiced. FF ¶¶ 80-85. Nova's alleged investment in NPC 16731 is based upon evidence prior to the alleged delay, and cannot constitute intervening rights. FF ¶¶ 81-82. Fresenius did not prove that Nova was adversely affected by the alleged delay. FF ¶¶ 83-85.

132. Fresenius did not prove that it was prejudiced. It has no intervening rights, let alone intervening rights that were adversely affected by the alleged delay. FF ¶¶ 86-87.

133. Prosecution laches does not apply "on the basis of claims that are not actually the subject of the litigation" (*Regents*, 2005 WL 3454107, at *24-26); here, it applies only to claim 14 (not the other claims or Groups 2-3). So it does not apply to Fresenius's allegations of intervening rights based only upon Nova's NPC 16731 in unasserted claim 12. FF ¶¶ 81, 86.

134. Fresenius did not establish by clear and convincing evidence that there was an unreasonable and unexplained delay in the prosecution of the '333 patent, let alone an egregious misuse of the patent system under the totality of the circumstances. FF ¶¶ 44-80.

135. Fresenius did not prove that it, Nova, or any other entity was prejudiced during and by an unreasonable and unexplained delay in the '333 patent's prosecution. FF ¶¶ 81-87.

IV. CONCLUSION

136. For the foregoing reasons, claim 14 of the '333 patent is not invalid or unenforceable. A proposed order entering judgment for Plaintiffs is attached.

MORRIS, NICHOLS, ARSHT & TUNNEL LLP

/s/ Derek J. Fahnestock

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March 5, 2018
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APPENDIX A

Shire Orphan Therapies LLC and Sanofi-Aventis Deutschland GmbH Fact Witnesses

Dr. Jochen Knolle, Ph.D.
(Tr. 265:20-309:20)

Dr. Knolle is a co-inventor on both the '333 and the '7,803 patents. He was employed at Hoechst from 1978-1998 as Head of the Medicinal Chemistry Laboratory and as Director of the Oligonucleotides and Peptides Department.

Due to an emergency surgery just before trial, Dr. Knolle testified via deposition.

Dr. Klaus Wirth, M.D.
(Tr. 444:15-481:20)

Dr. Wirth is a co-inventor on the '7,803 patent. He began his employment at Hoechst as a pharmacologist in 1984, and was working in the Pharmacology Department at the time that icatibant was invented.

Dr. Wirth is presently employed by Sanofi-Aventis Deutschland GmbH, a successor company of Hoechst.

Dr. Donald Kyle, Ph.D.
(Tr. 611:14-648:9)

Dr. Kyle was employed at Nova beginning in 1986. Dr. Kyle was Research Team Leader of the Kinin Antagonist Program at Nova from 1990-1995 and Director of Medicinal Chemistry from 1992-1995.

Dr. Kyle left Scios Inc., a successor company of Nova, in 1998.

Dr. Renate Wingefeld, Ph.D.
(Tr. 697:17-785:20)

Dr. Wingefeld oversaw the patent prosecution for both the ’333 and the ’7,803 patents from initial filing to issuance.

Dr. Wingefeld is presently employed by Sanofi-Aventis Deutschland GmbH, a successor company of Hoechst.

Dr. Irmgard Andresen, Ph.D.
(Tr. 796:17-802:23)

Dr. Andresen is Director of Shire's Global Medical Affairs Department and served as a Rule 30(b)(6) corporate representative on behalf of Shire Orphan Therapies LLC regarding the marketing of FIRAZYR as well as sales, prescriptions, market share, and projections of sales and prescriptions of FIRAZYR.

Aditi Dron
(Tr. 690:11-697:2)

Aditi Dron is Fresenius's regulatory affairs manager and served as a 30(b)(6) corporate representative on behalf of Fresenius Kabi USA on the topic of Fresenius's decision to pursue and develop a generic version of FIRAZYR.

Shire Orphan Therapies LLC and Sanofi-Aventis Deutschland GmbH Expert Witnesses

Dr. Allen P. Kaplan, M.D.
(Tr. 387:24-443:3)

Dr. Kaplan is a Clinical Professor of Medicine at the Medical University of South Carolina in the Division of Pulmonary Disease and Critical Care Medicine. Dr. Kaplan has over 40 years of experience treating patients with hereditary angioedema.

Dr. Loren Walensky, M.D., Ph.D.
(Tr. 485:19-610:18)

Dr. Walensky is a professor at Harvard Medical School, a principle investigator at the Dana Farber Cancer Institute, and a physician at Boston Children's Hospital. Dr. Walensky's research is focused on the design, synthesis, and characterization of peptides, as well as the application of those peptides to biochemical assays.

Dr. Gregory K. Bell, Ph.D.
(Tr. 649:1-689:24)

Dr. Bell is a group Vice President at Charles River Associates, a global economics and management consulting firm, and leads its global life sciences practice.

Dr. Joan Ellis, Ph.D.
(Tr. 786:7-795:23)

Dr. Ellis worked at the USPTO as a patent examiner in the biotechnology group for 8 years during the time that the ’333 patent was prosecuted, and then as an Administrative Patent Judge for over 11 years.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SHIRE ORPHAN THERAPIES LLC and SANOFI-AVENTIS DEUTSCHLAND GMBH,	)	
Plaintiffs,	)	C.A. No. 15-1102-GMS
v.	)	
FRESENIUS KABI USA, LLC,	)	
Defendant.	)	

[PROPOSED] FINAL JUDGMENT

From January 29 to February 2, 2018, the Court having conducted a bench trial in the above-referenced matter and having issued its Findings of Fact and Conclusions of Law:

IT IS HEREBY ORDERED AND ADJUDGED that, for the reasons set forth in the Findings of Fact and Conclusions of Law, the Court hereby enters judgment in favor of Plaintiffs Shire Orphan Therapies LLC and Sanofi-Aventis Deutschland GmbH (collectively, "Plaintiffs") and against Fresenius Kabi USA, LLC ("Fresenius" or "Defendant"), with respect to U.S. Patent No. 5,648,333 ("the '333 patent"), on Plaintiffs' claims and Defendant's counterclaims as follows:

1. The submission of ANDA No. 208317 by Fresenius to the FDA was an act of infringement of claim 14 of the '333 patent.

2. Claim 14 of the '333 patent is not invalid.

3. Claim 14 of the '333 patent is not unenforceable.

4. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any Food and Drug approval of Fresenius's ANDA No. 208317 shall not be on or before the expiration date of the

'333 patent (July 15, 2019), including any exclusivities and/or extensions to which Plaintiffs are or become entitled.

5. Pursuant to 35 U.S.C. § 271(e)(4)(B), Fresenius, as well as its officers, agents, servants, employees, attorneys, and those persons in active concert or participation with them, are permanently enjoined from commercially manufacturing, using, selling, or offering to sell within the United States, or importing into the United States, the product that is the subject of ANDA No. 208317 (including any amendments or supplements thereto), prior to the expiration of the '333 patent, including any exclusivities and/or extensions to which Plaintiffs are or become entitled.

6. Defendant's counterclaims seeking declaratory judgment of invalidity, non-infringement, and unenforceability of the '333 patent are dismissed with prejudice.

7. Pursuant to 21 C.F.R. § 314.107(e), Fresenius shall: (i) "within 14 days of the date of entry by the court" of this Final Judgment, submit a copy of this Final Judgment to the FDA; and (ii) provide confirmation of such communication to Plaintiffs' counsel of record within 7 days of Fresenius's submission.

8. Any motion for costs or attorney fees shall be filed within the timeframe provided in D. Del. LR 54.1 and Fed. R. Civ. P. 54(d).

9. All pending motions and other outstanding requests for relief not specifically addressed herein are DENIED.

SO ORDERED this _____ day of _____, 2018.

_____

Gregory M. Sleet
United States District Judge

CERTIFICATE OF SERVICE

I hereby certify that on March 5, 2018, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on March 5, 2018, upon the following in the manner indicated:

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/s/ Derek J. Fahnestock

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